Copy for the d signated Office (DO/US)

PCT/GB99/03721

:ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH
ROYAUME-UNI

Date of mailing (day/month/year)
28 June 2000 (28.06.00)

Applicant's or agent's file reference
REP05921WO

IMPORTANT NOTIFICATION

~~International application No.~~
PCT/GB99/03721

International filing date (day/month/year)
09 November 1999 (09.11.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
MICROSCIENCE LIMITED
12 St. James's Square
London SW1Y 4RB
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
MICROSCIENCE LIMITED
545 Eskdale Road
Winnersh Triangle
Wokingham
Berkshire RG41 5TU
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Jean-Marie McAdams

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 September 2000 (06.09.00)	
International application No. PCT/GB99/03721	**Applicant's or agent's file reference** REP05921WO
International filing date (day/month/year) 09 November 1999 (09.11.99)	**Priority date** (day/month/year) 09 November 1998 (09.11.98)
Applicant CROOKE, Helen, Rachel et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 May 2000 (18.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
REP05921WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03721	09/11/1999	09/11/1998
International Patent Classification (IPC) or national classification and IPC C12N15/31		
Applicant MICROSCIENCE LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/05/2000	21.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wimmer, G Telephone No. +49 89 2399 7347

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03721

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-16	as originally filed				

Claims, No.:

1-11	as received on	26/01/2001	with letter of	25/01/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03721

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 8-11; 1-7 (partially).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 8-11 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-11 (partially).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2
	No:	Claims 1, 3-6
Inventive step (IS)	Yes:	Claims
	No:	Claims 2
Industrial applicability (IA)	Yes:	Claims 1-7

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03721

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion.

1) As outlined in the international search report, the present application lacks unity of invention, and contains claims directed to 9 different inventions.
Since no additional search fees were paid by the applicant, the search report was established for claims regarding the tatA, tatB, tatC and tatE genes and proteins only, i.e. claims 1-11 only insofar as they refer to proteins with amino acid sequences according to SEQ IDs 11-14, 16, 18, 19 and 21, respectively.
Consequently, the international preliminary examination was also carried out with these restrictions.

2) The formulation of claim 8 is unclear, since the term "a pathogenicity island" is not defined with clear limits, thus allowing for wide interpretation. Furthermore, the formulation "...comprises a gene identified herein" is unclear, and it should be stated, which specific genes are intended. For this reason, and as described in detail under sections V.8 and V.9, the exact scopes of claim 8 cannot be assessed clearly. Novelty and the presence of an inventive step were therefore not examined for claim 8.

3) Due to the broadness of claim 1 (see details under section V.2), no meaningful examination of claims 9-11 with respect to novelty, inventive step and industrial applicability can be performed.

Re Item V

Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability.

The application does not meet the requirements of Art. 33 PCT since **claims 1 and 3-6 are not novel**, and **claim 2 does not contain an inventive step.**

1) Reference is made to the following documents (the document numbering corresponds to their order of citation in the international search report):

D1: SARGENT F. ET AL.: 'Overlapping functions of components of a bacterial Sec-independent protein export pathway' EMBO J., vol. 17, no. 13, 1 July 1998 (1998-07-01), pages 3640-3650, XP002133191

D4: 'tatC protein (mttB)' XP002133196 -& DATABASE GENBANK [Online] Accession No. AJ005830, 29 March 1999 (1999-03-29) SARGENT: 'E. coli tatABCD operon' XP002133197

D7: WEINER J.H. ET AL.: 'A novel and ubiquitous system for membrane targeting and secretion of cofactor-containing proteins.' CELL, vol. 93, 3 April 1998 (1998-04-03), pages 93-101, XP002133192

D11: BOYD E.F. & HARTL D.L.: 'Chromosomal regions specific to pathogenic isolates of Escherichia coli have a phylogenetically clustered distribution' J. BACTERIOL., vol. 180, no. 5, March 1998 (1998-03), pages 1159-1165, XP002133065

Novelty under Art. 33(2) PCT.

2) Claim 1 includes peptides encoded by the known tatA, tatB, tatC and tatE genes, or homologues thereof with at least 30% homology on nucleic acid or amino acid level, for therapeutic use.
The intended scope of protection is unduly large. It is clear that the skilled person will find hundreds of proteins with as little as 30% homology, most of which will be completely unrelated to the listed proteins. Furthermore, 30% homology on the nucleic acid level would e.g. mean an identity of less than every third base pair, and therefore, the terms of the claim also comprise proteins with not a single amino acid identity. Finally, the claim also seeks protection for "a functional fragment thereof". In the absence of a limitation of this term, the claim therefore also includes virtually *every* protein, any variation thereof, or any fragment, for any therapeutic use.
Clearly, this is not novel. Claims 1 and 3 therefore do not comply with Art. 33(2) PCT.

3) Polypeptides according to dependent claim 2 have been isolated and described (e.g. SEQ ID 13, which is the entire amino acid sequence of tatC, has been disclosed in D4). However, a medical use of said polypeptides has not been

disclosed in the prior art.
Claim 2 is therefore formally acknowledged to comply with Art. 33(2) PCT on the basis of first medical use.

4) Host cells according to claim 4 have been disclosed repeatedly in the prior art, e.g. in D7 (entire document) where bacterial cells express the mttA, B and C proteins, after transformation. Claim 4 therefore lacks novelty.

5) Concerning claim 5, most of any wild-type, or manipulated, bacteria are "means for the expression of a peptide according to claim 2" (interpretation of claim 5). Through this, any vaccine using microorganisms falls within the scope of claim 5, and, consequently, the claim lacks novelty.

6) Also, through the formulation of claim 1, subject-matter of claim 6 covers also vaccines with virtually any microorganism, since all microorganisms carry certain mutations (see section VIII.3 on clarity of the claim). Claim 6 is therefore not novel.

7) Although microorganisms specifically carrying deletions in the tatA and tatE gene have been described in the prior art, no use of these microorganisms as a vaccine has been described. However, the term "having a virulence gene deletion" is not clear (see sect. VIII.2). Novelty of the subject-matter of claim 7 could be acknowledged, provided that clarity of the claim were restored.

Inventive Step under Art. 33(3) PCT.

8) The bacterial tatA, tatB, tatC and tatE genes and proteins, as well as some of their physiological functions, had been extensively described in the prior art. However, no direct medical use had been described for them.
Applicants argue that the present application identifies these genes to be involved in bacterial virulence, and that this discovery can be exploited in the development of vaccines using attenuated bacteria. The applicants further argue that this application was not anticipated by the prior art, and therefore involves an inventive step. In the light of this, the applicants seek protection for accordingly attenuated bacteria (through deletion or mutation of one or more of the *tat* genes), for the

genes and proteins themselves for therapeutic use, and for related entities and methods.

While the prior art discloses crucial physiological functions of the tatA - tatE proteins (such as in protein transport), it does not suggest that deletions (or mutations) within these genes lead to a decrease in bacterial virulence. The IPEA therefore concurs with the applicants' view that the provision of bacteria with dysfunctional tatA, tatB, tatC or tatE genes, for use as a vaccine, involves an inventive step. Claim 7 therefore could possibly be viewed to comply with Art. 33(3) PCT, if clarity of the terms of the claim were restored (see sect. V.7 and VIII.2).

9) However, while it may not be obvious to the skilled person that dysregulation of these genes may lead to attenuated bacteria useful as vaccines, the genes (and their gene products) had been known to be involved in several crucial cellular pathways. Therefore, the skilled person would expect that e.g. deletion or mutation of these genes and proteins would be detrimental to the bacteria. A *general* applicability of the tatA-tatE genes and proteins was therefore obvious to the skilled person. Claim 2 is therefore not found to comply with Art. 33(3) PCT.

Moreover, as emphasized in the argumentation by the applicants, while physiological roles of the above listed proteins were known, the application shows an unexpected effect (that of decreased virulence) through the *deletion* of one (or more) of these genes in the context of the entire bacterium. It does *not*, by any means, show or indicate a novel or unexpected function of any of the proteins or genes *by itself.* Much less so does it disclose, through at least one example as required by Rule 5.1(v) PCT, general therapeutic applications thereof. Therefore, especially in the light of arguments raised by the applicants themselves, it appears that claims to the proteins for therapeutic use, variants, genes encoding them, host cells expressing the same etc., either fail to comply with Art. 33(3) PCT, or would alternatively appear to go well beyond the invention made by the applicants, and therefore also would not comply with Art. 5 PCT.

Re Item VIII

Certain observations and clarity.

1) The scope of the term "a functional fragment thereof" of claim 1 is open to speculation. This term allows for wide interpretation, since almost any peptidic fragment, up to a single amino acid, may be functional as e.g. an antigenic determinant.

2) The term "having a virulence gene deletion" in claim 7 is not clear. While it may be assumed that "having a virulence gene deletion in two genes" should signify "having deletions in two genes", neither the position (promoter, coding sequence, untranslated region) nor limits of the deletion are stated. In the absence of clarification, the claim would also comprise bacteria with deletions over wide regions of the chromosome, or with deletions which would not influence the expression of functional TatA or TatE proteins, and consequently, doubts as to the involvement of an inventive step would arise.
Similar applies to claim 6, wherein the term "having a virulence gene mutation" lacks clarity.

CLAIMS

1. A peptide encoded by an operon including any of the genes identified herein as *tatA*, tatB, *tatC*, *tatE*, *mdoG*, *creC*, *recG*, *yggN*, *eck1*, *iroD*, *iroC*, *iroE*, *mtd2* and *ms*1 to 16, obtainable from *E. coli* K1, or a homologue thereof in a Gram-negative bacterium, or a functional fragment thereof, for therapeutic use.

2. A peptide according to claim 1, comprising any of the amino acid sequences identified herein as SEQ ID NOS. 2, 5, 7, 9, 11, 12, 13, 14, 16, 18, 19, 21, 23, 24, 25, 26, 28, 29, 31, 32 and 35-48.

3. A polynucleotide encoding a peptide according to claim 1 or claim 2, for therapeutic use.

4. A host transformed to express a peptide according to claim 1 or claim 2.

5. A vaccine comprising a peptide according to claim 1 or claim 2, or the means for its expression.

6. A vaccine comprising a microorganism having a virulence gene mutation, wherein the gene encodes a peptide according to claim 1 or claim 2.

7. A vaccine according to claim 6, having a virulence gene deletion in two genes, wherein one gene encodes *tatA* and the other encodes *tatE*.

8. A vaccine according to claim 6, wherein the gene lies within a pathogenicity island, wherein the island comprises a gene identified herein.

9. Use of a product according to any of claims 1 to 4, or SEQ ID NO. 33, for screening potential drugs or for the detection of virulence.

10. Use of a product according to any of claims 1 to 4, for the manufacture of a medicament for use in the treatment or prevention of a condition associated with infection by a Gram-negative bacterium.

11. Use according to claim 10, wherein the bacterium is *E. coli*.

US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
REP05921WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/03721	09/11/1999	09/11/1998
Applicant		
MICROSCIENCE LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readble form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03721

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see additional sheet, invention 1.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (1-11) - partially, where applicable

A peptide encoded by an operon including tatA, tatB, tatC, tatD or by an operon including tatE (Seq. IDs 11-14,16,18,19,21) obtainable from E. coli K1, or a homologue thereof in a Gram-negative bacterium, or a functional fragment thereof, for therapeutic use.

Corresponding polynucleotide, recombinant host cells, vaccine containing said polypeptide, vaccine containing an attenuated pathogen in which the virulence gene encodes said peptide is mutated. Use in screening for potential drugs or detection of virulence; use in manufacture of medicament.

2. Claims: (1-11) - partially, where applicable

Idem as subject matter 1, but limited to mdoG (seq. ID 2).

3. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to creC (Seq. ID 5).

4. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to recG (Seq. ID 7).

5. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to yggN (Seq. ID 9).

6. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to eck1 (Seq. IDs 23-26).

7. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to iroC, iroD and iroE (Seq. IDs 28,29,31,32).

8. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to aslA/hemY (Seq. ID 33).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to mtd2/ms1-16 (Seq. IDs 35-48).

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	-& DATABASE SWISSPROT [Online] Accession No. P27857, 15 July 1998 (1998-07-15) "tatC protein (mttB)" XP002133196 the whole document	1-4
P,X	-& DATABASE GENBANK [Online] Accession No. AJ005830, 29 March 1999 (1999-03-29) SARGENT: "E. coli tatABCD operon" XP002133197 cited in the application the whole document	1-4
X	--- DATABASE GENBANK [Online] Accession No. P25895, 1 November 1997 (1997-11-01) CHUNG E.: "E. coli protein YBEC from CRB-LIPA intergenic region" XP002133198 the whole document	1-4
A	--- WEINER J.H. ET AL.: "A novel and ubiquitous system for membrane targeting and secretion of cofactor-containing proteins." CELL, vol. 93, 3 April 1998 (1998-04-03), pages 93-101, XP002133192 the whole document	1-11
A	--- BOGSCH E.G. ET AL.: "An essential component of a nove bacterial protein export system with homologues in plastids and mitochondria" J. BIOL. CHEM., vol. 273, no. 29, 17 July 1998 (1998-07-17), pages 18003-19006, XP002133193 the whole document	1-11
A	--- CIESLEWICZ M. & VIMR E.: "Thermoregulation of kpsF, the First Region 1 gene in the kps locus for polysialic acid biosynthesis in E. coli K1" J. BACTERIOLOGY, vol. 178, no. 11, June 1996 (1996-06), pages 3212-3220, XP000877094 the whole document ✓	1-11
	--- -/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VANN W.F. ET AL.: "Purification and characterization of the Escherichia coli K1 neuB gene product N-acetylneuraminic acid synthase" GLYCOBIOLOGY, vol. 7, no. 5, 1997, pages 697-701, XP000877095 the whole document ---	1-11
A	BOYD E.F. & HARTL D.L.: "Chromosomal regions specific to pathogenic isolates of Escherichia coli have a phylogenetically clustered distribution" J. BACTERIOL., vol. 180, no. 5, March 1998 (1998-03), pages 1159-1165, XP002133065 the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

International Application No
PCT 99/03721

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/31 C12N1/21 C07K14/245 A61K38/16 A61K39/108
//(C12N15/31,C12R1:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SARGENT F. ET AL.: "Overlapping functions of components of a bacterial Sec-independent protein export pathway" EMBO J., vol. 17, no. 13, 1 July 1998 (1998-07-01), pages 3640-3650, XP002133191 the whole document	1-4
X	-& DATABASE SPTREMBL [Online] Accession No. O65938, 1 August 1998 (1998-08-01) "tatA protein (mttA1)" XP002133194 the whole document	1-4
X	-& DATABASE SPTREMBL [Online] Accession No. O69415, 1 August 1998 (1998-08-01) "tatB protein (mttA2)" XP002133195 the whole document	1-4

-/--

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2000	26. 06. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/31, 1/21, C07K 14/245, A61K 38/16, 39/108

A2

(11) International Publication Number: WO 00/28038

(43) International Publication Date: 18 May 2000 (18.05.00)

(21) International Application Number: PCT/GB99/03721

(22) International Filing Date: 9 November 1999 (09.11.99)

(30) Priority Data:

9824569.9	9 November 1998 (09.11.98)	GB
9824570.7	9 November 1998 (09.11.98)	GB
9827814.6	17 December 1998 (17.12.98)	GB
9827815.3	17 December 1998 (17.12.98)	GB
9827816.1	17 December 1998 (17.12.98)	GB
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9900708.0	13 January 1999 (13.01.99)	GB
9900710.6	13 January 1999 (13.01.99)	GB
9900711.4	13 January 1999 (13.01.99)	GB
9901915.0	28 January 1999 (28.01.99)	GB

(71) Applicant *(for all designated States except US)*: MICROSCIENCE LIMITED [GB/GB]; 12 St. James's Square, London SW1Y 4RB (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CROOKE, Helen, Rachel [GB/GB]; Imperial College School of Medicine at the Hammersmith Campus, Dept. of Infectious Diseases, Du Cane Road, London W12 0NN (GB). CLARKE, Enda, Elizabeth [GB/GB]; Imperial College School of Medicine at the Hammersmith Campus, Dept. of Infectious Diseases, Du Cane Road, London W12 0NN (GB). EVEREST, Paul, Howard [GB/GB]; Imperial College School of Medicine at the Hammersmith Campus, Dept. of Infectious Diseases, Du Cane Road, London W12 0NN (GB). DOUGAN, Gordon [GB/GB]; Imperial College School of Medicine at the Hammersmith Campus, Dept. of Infectious Diseases, Du Cane Road, London W12 0NN (GB). HOLDEN, David, William [GB/GB]; Imperial College School of Medicine at the Hammersmith Campus, Dept. of Infectious Diseases, Du Cane Road, London W12 0NN (GB). SHEA, Jacqueline, Elizabeth [GB/GB]; Imperial College School of Medicine at the Hammersmith Campus, Dept. of Infectious Diseases, Du Cane Road, London W12 0NN (GB). FELDMAN, Robert, Graham [GB/GB]; Imperial College School of Medicine at the Hammersmith Campus, Dept. of Infectious Diseases, Du Cane Road, London W12 0NN (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: VIRULENCE GENES AND PROTEINS, AND THEIR USE

(57) Abstract

The present invention is based on the identification of a series of virulence genes in *E. coli* K1, the products of which may be implicated in the pathogenicity of the organism. The identificaiton of the genes allows them, or their expressed products, to be used in a number of ways to treat infection.

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(51) International Patent Classification 7 :
C12N 15/31, 1/21, C07K 14/245, A61K 38/16, 39/108 // (C12N 15/31, C12R 1:19)

A3

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(54) Title: VIRULENCE GENES AND PROTEINS, AND THEIR USE

(57) Abstract

The present invention is based on the identification of a series of virulence genes in *E. coli* K1, the products of which may be implicated in the pathogenicity of the organism. The identificaiton of the genes allows them, or their expressed products, to be used in a number of ways to treat infection.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03721

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/31 C12N1/21 C07K14/245 A61K38/16 A61K39/108
//(C12N15/31,C12R1:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SARGENT F. ET AL.: "Overlapping functions of components of a bacterial Sec-independent protein export pathway" EMBO J., vol. 17, no. 13, 1 July 1998 (1998-07-01), pages 3640-3650, XP002133191 the whole document	1-4
X	-& DATABASE SPTREMBL [Online] Accession No. O65938, 1 August 1998 (1998-08-01) "tatA protein (mttA1)" XP002133194 the whole document	1-4
X	-& DATABASE SPTREMBL [Online] Accession No. O69415, 1 August 1998 (1998-08-01) "tatB protein (mttA2)" XP002133195 the whole document	1-4

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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2000	26. 06. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	-& DATABASE SWISSPROT [Online] Accession No. P27857, 15 July 1998 (1998-07-15) "tatC protein (mttB)" XP002133196 the whole document	1-4
P,X	-& DATABASE GENBANK [Online] Accession No. AJ005830, 29 March 1999 (1999-03-29) SARGENT: "E. coli tatABCD operon" XP002133197 cited in the application the whole document	1-4
X	DATABASE GENBANK [Online] Accession No. P25895, 1 November 1997 (1997-11-01) CHUNG E.: "E. coli protein YBEC from CRB-LIPA intergenic region" XP002133198 the whole document	1-4
A	WEINER J.H. ET AL.: "A novel and ubiquitous system for membrane targeting and secretion of cofactor-containing proteins." CELL, vol. 93, 3 April 1998 (1998-04-03), pages 93-101, XP002133192 the whole document	1-11
A	BOGSCH E.G. ET AL.: "An essential component of a nove bacterial protein export system with homologues in plastids and mitochondria" J. BIOL. CHEM., vol. 273, no. 29, 17 July 1998 (1998-07-17), pages 18003-19006, XP002133193 the whole document	1-11
A	CIESLEWICZ M. & VIMR E.: "Thermoregulation of kpsF, the First Region 1 gene in the kps locus for polysialic acid biosynthesis in E. coli K1" J. BACTERIOLOGY, vol. 178, no. 11, June 1996 (1996-06), pages 3212-3220, XP000877094 the whole document	1-11

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VANN W.F. ET AL.: "Purification and characterization of the Escherichia coli K1 neuB gene product N-acetylneuraminic acid synthase" GLYCOBIOLOGY, vol. 7, no. 5, 1997, pages 697-701, XP000877095 the whole document ---	1-11
A	BOYD E.F. & HARTL D.L.: "Chromosomal regions specific to pathogenic isolates of Escherichia coli have a phylogenetically clustered distribution" J. BACTERIOL., vol. 180, no. 5, March 1998 (1998-03), pages 1159-1165, XP002133065 the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03721

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see additional sheet, invention 1.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (1-11) - partially, where applicable

A peptide encoded by an operon including tatA, tatB, tatC, tatD or by an operon including tatE (Seq. IDs 11-14,16,18,19,21) obtainable from E. coli K1, or a homologue thereof in a Gram-negative bacterium, or a functional fragment thereof, for therapeutic use.

Corresponding polynucleotide, recombinant host cells, vaccine containing said polypeptide, vaccine containing an attenuated pathogen in which the virulence gene encodes said peptide is mutated. Use in screening for potential drugs or detection of virulence; use in manufacture of medicament.

2. Claims: (1-11) - partially, where applicable

Idem as subject matter 1, but limited to mdoG (seq. ID 2).

3. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to creC (Seq. ID 5).

4. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to recG (Seq. ID 7).

5. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to yggN (Seq. ID 9).

6. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to eck1 (Seq. IDs 23-26).

7. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to iroC, iroD and iroE (Seq. IDs 28,29,31,32).

8. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to aslA/hemY (Seq. ID 33).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: (1-11) - partially, where applicable

Idem as subject-matter 1, but limited to mtd2/ms1-16 (Seq. IDs 35-48).